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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,162	07/10/2003	Laszlo Vigh	CytRx/009 DIV2	4065

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,162	VIGH ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/11/09 has been entered.

2. Applicant's arguments filed 5/11/09 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 20-22 and 26-32 are pending in this office action.

5. The rejection of claims **20-22 and 26-32** under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **17-34** of (U.S. 7148239) for the reasons made in Paper No. 20080611 is withdrawn because the parent 08/860582 was restricted and '239 and '162 were simultaneously filed.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites the limitation "host" in claim 20. There is insufficient antecedent basis for this limitation in amended base claim 20.

7. Claims 20-22, 26-29 and 31-32 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus

because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The mere fact that Applicant may have discovered one type of derivative of the compound of formula I to be effective in treating one specific disease is not sufficient to claim the entire genus of the compound of formula I.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species

encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

8. Claims 20-22 and 26-32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating heat stress cardiac ischemia with hydroxylamine, does not reasonably provide enablement for a method of treating undefined or generic conditions merely associated with the activity of the chaperone system in a cell or associated with the injury of a cell membrane or cell organellum,…. administering to a cell that is exposed to a physiological stress , cell membrane……." with a chemical compound to increase the expression of the molecular chaperon by the cell beyond the amount induced by the physiological stress, wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons made of record in Paper No. 20080611 and as follows.

Applicant argues that "[t]he Office does not dispute that Applicants have demonstrated that the compounds provided in the genus of amended claim 20 are effective in producing a desirable response in the heat-shock experiments of the pending application, as well as in related issued U.S. Patent Nos. 6,653,326 and 7,148,239". Applicant argues that "Exhibit A (Gething et al., Nature, 355, 33-45,

(1992)) is one of many publications that characterize heat-shock proteins as being well known molecular chaperones which are involved in the cellular response of organisms to, inter alia, heat shock. In addition, Exhibit A illustrates that one of ordinary skill would recognize and understand that the proteins may be induced under a variety of other stress conditions (see Exhibit A, p. 35, cols. 1-2)". Further, Applicant argues that Exhibit B (Welch, Cell Stress & Chaperones, 1(2): 109-115, (1996)), "protein folding and assembly inside the cell is mediated by a class of proteins now commonly termed molecular chaperones." (See Exhibit B, p. 109, col. 1) and Table 1, entitled "Diseases involving defective protein folding" lists a relatively wide variety of diseases that are known to involve defective protein folding and/or trafficking.

In response as stated in the last office action of record each application is examined on its own merits. The claims fail to identify which chaperone system is specifically being addressed. Secondly none of the diseases are related and none of the diseases appear to be due to a dysfunction of any generic compound recited in the claims. Furthermore in order to provide support for the claimed methods comprising (i) treating a disease connected to the function of chaperon, (ii) treating a disease associated with the injury of the cell membrane and (iii) administering an effective amount of a hydroxylamine derivative of formula I, one of skill in the art would require a significant amount of experimentation in order to first identify which chaperon system is affected, which disease is associated with the particular chaperon system, how this association relates with injury of the cell, and then a means of treatment.

As discussed in the last office action, these diseases are so diverse in nature that one cannot envision any treatment with the compounds of claims 20 and 30.

For example, treatment of viral disease, bacteria, tumor and immune disease alone is cumbersome. Immune diseases can further occur anywhere on the body and, for example, there is no one particular drug capable of treating every cancer known in the art, or immune disease, bacteria infection and allergic disease as envisioned by the claims.

Taking Applicant's submission as evidence "Welch et al. Influence of molecular and chemical chaperones" (Appendix B) teaches the involvement of different proteins in diseases that involves defective protein folding (see page 110, Table I). Thus showing and confirming that no one chemical drug is capable of treating the numerous diseases encompassed by the claimed invention supports the rejection of record.

In arguendo Applicant has not shown that even the preferred embodiment compounds of formula I (i.e., hydroxylamine) are capable of treating all the diseases encompassed by the claims. All that is confirmed by the prior art is that different molecular mechanisms/proteins are responsible for different disease states.

Applicant's arguments have been fully considered but they are not persuasive for the reasons given above.

In summary:

The Breadth of the Claims

The instant claims are directed to a "method of treating a condition associated with the activity of the chaperone system in a cell or associated with the injury of a cell

membrane or cell organellum,…. administering to a cell that is exposed to a physiological stress , cell membrane……..” with a chemical compound to increase the expression of the molecular chaperon by the cell beyond the amount induced by physiological stress, wherein the chemical compound is one or more of a hydroxylamine derivative represented by formula I.

The instant claims are also directed to treating allergic diseases, immune diseases, autoimmune diseases, diseases of viral or bacterial origin, tumorous, skin and/or mucous diseases, epithelial disease of renal tubulus, atherosclerosis, coronarial disease, pulmonary hypertonia, cerebrovascular ischemia, stroke, or traumatic head injury with an effective amount of a chemical compound of formula I (see also bystress.com). For example, treating a wide variation of tumors is encompassed by the claims (e.g., breast, lung pancreatic brain cancer, etc.).

The Nature of the Invention

The nature of the invention relates to using the compound of formula I for the treatment of a very wide variation of diseases that are associated with the functions of chaperon proteins and injury of the membrane. Several examples of are given in the specification on pages 112-134, wherein the use of different types of hydroxylamine compounds are employed. However, the showing of induction of heat shock proteins with these particular compounds do not provide adequate support to enable one to practice the instant methods. See Applicants’ own admission (see para 00353, pg 21 of the published application) using the specification as a dictionary. “The mechanism(s) by

which stress (physical, pathophysiological, etc.) is detected as a signal and transduced to the transcriptional apparatus is hitherto unknown". Identifying one pathway does not necessarily yield treatment for a wide variation of diseases. These diseases are very complex and usually have multiple etiological factors involved.

Guidance

The specification only discloses examples on pages 80-85 and the making of formulations on pages 85-91 related to induction of heat shock proteins and/ or treatment of heat stress cardiac ischemia, yet fails to show how diseases in general may be treated with the claimed compound of formula I. The specification has not provided direction in the form of representative examples to show that the combinations of the functional groups claimed would have efficacy in treating a wide variation of diseases as claimed. The use of the compounds of formula I to treat a wide variety of stress conditions (see enclosed different types of physiological stress) is not reasonable because there is no one drug known in the art capable of treating every disease known in the art. For example, cisplatinum (a known anti cancer agent) can only treat specific cancers and when the cancers do metastasize they require other drugs. In addition the Cecil Text book of Medicine teaches that each specific type of cancer has unique biological and chemical features that must be appreciated for proper treatment (see page 1004; as it especially relates to claim 21). Therefore one skilled in the art would not have expected that administering the claim generic compounds would result in the treatment of a wide variation of cancers. Thus, it is beyond the skill in the art to envision

one drug that will treat all of these various stress forms, such as stroke, gastric problem, eating, pain, sleep disorder etc.

The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure and Working Examples

In order to provide support for the claimed methods comprising treatments with a hydroxylamine compound of formula I, one of skill in the art would require a significant amount of experimentation in order to find which disease is associated with a chaperon system, and then associate how any injury of the cell can be then be subsequently treated. The nature of the invention is extremely complex in that it encompasses the use of the compounds of formula I for treating various unrelated pathological conditions such as neoplastic disease (which itself encompasses a very wide variety of different types of pathology). As defined, neoplastic diseases are different diseases that start and evolve each in its own manner and trigger variable responses within the organism depending upon the pathologies of the neoplastic process. The clinical incidence of the different cancers is spread throughout the human life span, with regional differences for each cancer. See CiteSeer abstract (already of record). Additionally, each particular neoplastic disease/infection caused by a pathogenic microorganism or all autoimmune disease has its own specific characteristics and etiology. The unpredictability observed with single agent therapy to treat a very wide range of diseases is substantial. The broad recitation " neoplastic disease/infection caused by pathogenic microorganism or autoimmune disease or dermatosis" is inclusive of many conditions that presently have

no established successful therapies. Therefore, because administration of the claimed compounds and test model systems required to determine whether or not a compound would treat any definable disease state is unpredictable, because of the state of the art and the limited guidance provided within the instant specification using one drug for the treatment of so many diseases connected with function of a chaperon system is not reasonable, and because induction of heat stress proteins alone provides no nexus to treat any disease state, one of ordinary skill in the art would not know how to use the invention as currently broadly claimed without requiring undue experimentation to discover such after-the-fact.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618
7/14/09

/Robert C. Hayes/
Primary Examiner, Art Unit 1649